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the amino acid sequence of an enzyme, thus interfering either with its ability to bind or release intermediates or with its stability. (ref 3, 4) Another consequence of a point mutation is the deletion of an entire coding sequence (exon) because of a single mutation in that exon (ref 5) or in an adjacent untranscribed sequence (intron) (ref 6).

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If a mutation does not alter an antigenically recognized site on an enzyme, the relative amount of nonfunctional enzyme can be calculated by quantitating the mass of enzymatic protein that cross-reacts with specific antibodies to the normal (purified) enzymatic protein (called cross-reacting immunologic material [CRIM]) and then comparing this value with the catalytic activity of the enzyme. This technique has confirmed the presence of a dysfunctional enzyme as the cause of certain CRIM-positive familial cases of porphyria. CRIM-negative familial cases are caused by the lack of enzyme production by one allele or by sufficient enzymatic disruption to prevent recognition by an antibody.

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Erythropoietic protoporphyria (EPP) (see below) is an autosomal dominant disease in which ferrochelatase activity is reduced by approximately 50 percent. It also exists in a so-called homozygous recessive form that is more severe and begins earlier in life. In patients with this condition, enzymatic activity is reduced to less than 10 percent of normal. If the parents of such a patient are not related, it is likely that the two defective alleles have distinct, nonidentical mutations. This hypothesis has been confirmed in a family in which two different point mutations, each carried by one parent, were isolated in the propositus. (ref 7) Thus, such phenotypically homozygous individuals should more correctly be classified as double heterozygotes.

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It is likely that double heterozygosity also occurs in familial porphyria cutanea tarda (PCT), in which genetic heterogeneity is also seen, and in hepatoerythropoietic porphyria (HEP), its more severe, recessive counterpart. (ref 8) Dual porphyrias, in which more than one enzyme in the sequence is affected in a single kindred, have also been documented. (ref 9, 10, 11)

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Our greater understanding of the molecular biology of porphyrin synthesis has led not only to advances in clinical evaluation and diagnosis but also to the use of effective therapy. Treatment with the heme molecule represses the hepatic rate-limiting enzyme ALA synthetase, thereby reducing the overproduction of porphyrin precursors in the liver, with consequent relief of symptoms (see below).

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Hepatic Porphyrias